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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
COLLINS, CYNTHIA E	

ART UNIT	PAPER NUMBER
1638	

DATE MAILED: 10/21/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/737,476	FRENKEN ET AL.	
	Examiner	Art Unit	
	Cynthia Collins	1638	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- *Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.*
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 August 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-14* is/are pending in the application.

4a) Of the above claim(s) *8 and 10-13* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-7,9 and 14* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Applicant's submission filed on August 5, 2004 has been entered.

Claims 1, 2, 9 and 14 are currently amended.

Claims 8 and 10-13 are withdrawn.

Claims 1-14 are pending.

Claims 1-7, 9 and 14 are examined.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

All previous objections and rejections not set forth below have been withdrawn.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 1 and claims 2-7 and 9 dependent thereon are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 1 provides for the use of a method for producing an antibody or an active fragment thereof, but, since the claim does not set forth any steps involved in the method/process, it is unclear what method/process applicant is intending to encompass. A claim is indefinite where it merely recites a use without any active, positive steps delimiting how this use is actually practiced.

Claim 1 and claims 2-7 and 9 dependent thereon are rejected under 35 U.S.C. 101 because the claimed recitation of a use, without setting forth any steps involved in the process,

results in an improper definition of a process, i.e., results in a claim which is not a proper process claim under 35 U.S.C. 101. See for example *Ex parte Dunki*, 153 USPQ 678 (Bd.App. 1967) and *Clinical Products, Ltd.* v. *Brenner*, 255 F. Supp. 131, 149 USPQ 475 (D.D.C. 1966).

Claim Rejections - 35 USC § 102

Claims 1, 3, 7, 9 and 14 remain rejected under 35 U.S.C. 102(b) as being anticipated by Magnuson et al. (Protein Expression and Purification, 1996, Vol. 7, pages 220-228), for the reasons of record set forth in the office action mailed April 8, 2004.

Applicants' arguments filed August 5, 2004, have been fully considered but they are not persuasive.

Applicants argue that Magnuson does not anticipated the rejected claims because the successful excretion of monoclonal antibody heavy chains in a tobacco cell suspension is not the same as the production of VHH in plant cellular compartments as claimed. Applicants further argue that the cell suspension culture and conditions of culturing disclosed in Magnuson would not teach one how to achieve production of a VHH in a plant cellular compartment because cell suspension conditions are very different from growth conditions in an actual plant. (reply page 6)

The rejection is maintained because claims 1, 3, 7 and 9 recite no method steps that require the growth of a multicellular plant such that the claimed methods cannot be distinguished from the method taught by Magnuson on this basis. The rejection is also maintained because the successful excretion of monoclonal antibody heavy chains in a tobacco cell suspension necessarily requires the production of a heavy chain immunoglobulin in a plant cellular compartment, as excretion of proteins from cells requires their production in the endoplasmic

reticulum cellular compartment prior to their excretion. The rejection is additionally maintained because the introduction of a DNA sequence into a plant as recited in claim 14 necessarily requires the introduction of the DNA sequence into a plant cell, as the introduction of DNA occurs at the cellular level.

Claims 1, 2, 7, 9 and 14 remain rejected under 35 U.S.C. 102(b) as being anticipated by Casterman et al. (WO 94/04678, 3 March 1994, Applicant's IDS), for the reasons of record set forth in the office action mailed April 8, 2004.

Applicants' arguments filed August 5, 2004, have been fully considered but they are not persuasive.

Applicants argue that a mere reference to another article that teaches bits and pieces of items required to practice the claimed invention does not translate to an enabling disclosure for the cited reference, and Applicants point in particular to MPEP 2131.01 as stating that extra references may be relied upon to show a primary reference contains an "enabled disclosure" when the claimed composition or machine is disclosed identically by the reference. Applicants also argue that a reference that merely postulates that something could be done does not identically disclose the invention, and Applicants point out that if attempts at performing the invention were unsuccessful before the date of invention, then a reference that merely suggests that something could be done, but does not actually put it into practice, does not contain an enabling disclosure. (reply pages 6-7).

The rejection is maintained because the method disclosed by Casterman et al. is identical to the claimed method. The Examiner maintains that because claims 1, 2, 7 and 9 recite no

method steps, the claimed methods cannot be distinguished from the method taught by Casterman et al. The Examiner also maintains that the sole method step recited in the currently amended claims, the introduction of a DNA sequence encoding a heavy chain antibody into a plant required by claim 14, is taught by Casterman et al. The Examiner additionally maintains that the step of introducing a DNA sequence into a plant was fully enabled and was in fact routine at the time the instant Applicant was filed. The Examiner further maintains that the expression in plants of heavy chain immunoglobulin polypeptides in the absence of light chain immunoglobulin polypeptides was fully enabled as discussed *infra*.

Applicants additionally argue that it is clear that neither Casterman et al. nor Hiatt et al. teach all the limitations of the claimed invention, and that therefore neither of these references is prior art under 35 USC 102 (reply page 7).

The Examiner maintains that the claims were rejected under 35 U.S.C. 102(b) as being anticipated by Casterman et al. (WO 94/04678, 3 March 1994, Applicant's IDS). Accordingly, Applicants' assertion that Hiatt et al. is not prior art under 35 USC 102 is not germane to the instant rejection.

Applicants further argue that the mere fact that Casterman et al. mentions Hiatt et al. does not mean that Casterman has put into practice the production of heavy chain antibodies in plants (reply page 7).

The Examiner maintains that the claims as currently amended do not require the production of heavy chain antibodies in plants. The Examiner further maintains that it is not

required that Casterman et al. exemplify the production of heavy chain antibodies in plants as the production of heavy chain antibodies in plants was fully enabled at the at the time the instant application was filed, as evidenced by Hiatt et al. discussed *infra*.

Applicants point out that Hiatt et al. concerns the assembly of kappa and gamma chains in plants to form a functional complete murine antibody comprising a heavy and a light chain, and Applicants maintain that Hiatt does not disclose the production of heavy chain only immunoglobulins in plants (reply page 7).

The Examiner maintains that the claims as currently amended do not require the production of heavy chain only immunoglobulins in plants. The Examiner points out that claims 1, 2, 7 and 9 recite no method steps at all, and claim 14 requires only the introduction of a DNA sequence encoding a heavy chain antibody into a plant. The Examiner also points out that even the preamble, which is not interpreted as limiting the claimed method, does not refer to the production of heavy chain only immunoglobulins in plants; the preamble refers only to the production of an antibody which is a heavy chain immunoglobulin devoid of a variable light chain domain in a cellular compartment of a plant. The production of an antibody which is a heavy chain immunoglobulin devoid of a variable light chain domain in a cellular compartment of a plant does not exclude the production of a variable light chain domain in the same plant, it merely refers to the heavy chain immunoglobulin as being devoid of a variable light chain domain upon its production.

The Examiner also maintains that Hiatt et al. in fact successfully introduced into a plant and expressed a DNA sequence encoding only a heavy chain immunoglobulin (Hiatt et al.,

Nature, 1989, Vol. 342, pages 76-79, see page 77 Table 1 and Figure 1). Hiatt et al. teach two different types of plants transformed with and expressing a DNA sequence encoding only a heavy chain immunoglobulin: a plant transformed with a DNA sequence encoding a heavy chain immunoglobulin with no leader sequence (γNL), and a plant transformed with a DNA sequence encoding a heavy chain immunoglobulin with a leader sequence (γL) (page 77 Table 1 and Figure 1).

Applicants also point in particular to the discussion at page 2 in the specification regarding several groups that had reported the functional expression of murine monoclonal antibodies in plants. Applicants maintain that it had been reported in practice that better yield are achieved with plants transformed with complete murine antibodies rather than with small fragments, and that the yield of each chain is increased in plants expressing both gamma and kappa, indicating that assembly of the gamma-kappa complex might enhance stability. Applicants argue that the skilled artisan having read this passage would be led away from applying the methods of Hiatt et al. to the production of heavy chain antibodies in plants, particularly in view of the difficulties known in the art in expressing functional heavy chain fragments in plants. (reply page 8)

Applicants further maintain that a prior art reference must be considered in its entirety, i.e., as a whole, including portions that would lead away from the claimed invention, *WLL . Gore & Associates, Inc. v. Garlock, Inc.*, 72 l F.2d 1540, 220 USPQ 303 (Fed. Cir. 1983), and that it is improper to combine references where the references teach away from their combination. *In re Grasselli*, 713 F.2d 731, 743, 2 18 USPQ 769,779 (Fed. Cir. 1983). Applicants also note that

there is no indication in Hiatt et al. that the small amount of heavy chain actually produced in the absence of light chain is functional. Applicants further maintain that evidence of unpredictability in the art is indeed germane to the instant rejection, since it appears that the Examiner, in principle, has made an obviousness rejection by combining Casterman et al. and Hiatt et al. Applicants maintain that neither of these references teaches how to put the claimed invention into practice, and that Hiatt et al. actually teaches away from the production of heavy chain only immunoglobulins, since the reference discloses that the heavy chain expressed alone appears to be significantly less stable than when coexpressed with light chain. (reply pages 8-9)

Applicants' arguments referring to the issue of obviousness under 35 USC 103, i.e. *WLL . Gore & Associates, Inc. v. Garlock, Inc.*, *In re Grasselli*, and the art as teaching away from the claimed invention, are moot with respect to the instant rejection of the claims under 35 USC 102, because Casterman et al. teach a method for modifying a plant to produce an antibody by introducing into a plant a DNA sequence encoding a heavy chain immunoglobulin obtainable from camelids, and because introducing into a plant and expressing a DNA sequence encoding a heavy chain immunoglobulin obtainable from camelids was fully enabled at the time the instant application was filed, as evidenced by Hiatt et al. discussed *supra*. The rejection at issue here is the rejection of claims 1, 2, 7, 9 and 14 under 35 U.S.C. 102(b) as being anticipated by Casterman et al.; there is NO outstanding rejection of record of claims 1, 2, 7, 9 and 14 under 35 U.S.C. 103(a) as being obvious over Casterman et al. in view of Hiatt et al. Furthermore, all outstanding rejections of record that were made under 35 U.S.C. 103(a) are discussed *infra*.

Applicants' arguments are also directed to limitations that are not recited in the rejected claims. The rejected claims recite no limitations concerning the yield or stability of the

immunoglobulin, and the rejected claims do not require the production of a heavy chain that is functional in the absence of light chain, or the production of heavy chain only immunoglobulins. Claims 1, 2, 7 and 9 recite no method steps at all, and claim 14 requires only the introduction of a DNA sequence encoding a heavy chain antibody into a plant.

Claim Rejections - 35 USC § 103

Claim 4 remains rejected under 35 U.S.C. 103(a) as being unpatentable over either of Magnuson et al. (Protein Expression and Purification, 1996, Vol. 7, pages 220-228) or Casterman et al. (WO 94/04678, 3 March 1994, Applicant's IDS), in view of Owen et al. (Biotechnology, Vol. 10, pages 790-794, July 1992), for the reasons of record set forth in the office action mailed April 8, 2004.

Applicants' arguments filed August 5, 2004, have been fully considered but they are not persuasive.

Applicants point out that Magnuson et al. teach expression of heavy chain immunoglobulin in a cell suspension culture which does not represent production in compartments of a real plant. Applicants maintain that the conditions of growth in a cell suspension culture are much more controlled and easily optimized for protein production, whereas expression in a compartment of a plant is more difficult and subject to more complex processes, such that the mere expression in a cell suspension is not the same as the successful production of VHH in plant cellular compartments. (reply page 10)

The Examiner maintains that Applicants arguments are directed to limitations that are not recited in the rejected claims. The rejected claims recite no limitations directed to the production

of antibodies in the "compartments of a real plant"; rather, the rejected claims recite that production occurs in a "cellular compartment of a plant". The successful excretion of monoclonal antibody heavy chains in a tobacco cell suspension taught by Magnuson et al. necessarily requires the production of a heavy chain immunoglobulin in a plant cellular compartment, as excretion of proteins from cells requires their production in the endoplasmic reticulum cellular compartment prior to excretion.

Applicants also point out that although Casterman et al. mention that the disclosed VHH may be produced in plants, this was a mere invitation to experiment and not an enabling disclosure of the production of a VHH in a plant cellular compartment. Applicants maintain that, as discussed at length above and incorporated herein for convenience, the mere reference to the plant promoters disclosed in Hiatt et al. does not provide an enabling disclosure, particularly given that Hiatt et al. teaches away from the production of heavy chain only immunoglobulins in plants, and further given the state of the art at the time. (reply page 10)

As discussed above, the Examiner maintains that Casterman et al. is fully enabled, as evidenced by Hiatt et al.'s successful production of two different transgenic plant lines that express only immunoglobulin heavy chain polypeptides. Further, the teachings of Hiatt et al. are directed solely to the production in plants of mammalian immunoglobulin proteins which comprise both heavy and light chain polypeptides in their native state. Hiatt et al. makes no reference to the production in plants of camelid immunoglobulins which comprise only heavy chain polypeptides in their native state. Accordingly concerns about the stability or yield of mammalian heavy chain polypeptides produced in plant cells the absence of mammalian light

chain polypeptides would not teach away from the production in plant cells of camelid heavy chain polypeptides, as camelid heavy chain polypeptides are natively produced in the absence of light chain polypeptides.

Applicants also argue that Owen et al. does not make up for the deficiencies of Magnuson et al. and Casterman et al., since Owen et al. also provide no disclosure of heavy chain only antibodies in plants (reply pages 10-11)

The Examiner maintains that Owen et al. was not cited for the disclosure of heavy chain only antibodies in plants. As set forth at pages 5-6 of the office action mailed April 8, 2004, Casterman et al. was cited for disclosing the expression in plants of heavy chain only antibodies, and Owen et al. was cited for disclosing the expression in plants of a DNA sequence encoding a single-chain Fv recombinant immunoglobulin capable of specific binding with an antigen that is a protein present in a plant, such that it would have been obvious to one skilled in the art at the time the invention was made to express in a plant any type of immunoglobulin capable of specific binding with an antigen that is a protein present in a plant.

Claim 5 remains rejected under 35 U.S.C. 103(a) as being unpatentable over either of Magnuson et al. (Protein Expression and Purification, 1996, Vol. 7, pages 220-228) or Casterman et al. (WO 94/04678, 3 March 1994, Applicant's IDS), in view of Le Gall et al. (Applied and Environmental Microbiology, Vol. 64, No. 11, pages 4566-4572, November 1998), for the reasons of record set forth in the office action mailed April 8, 2004.

Applicants' arguments filed August 5, 2004, have been fully considered but they are not persuasive.

Applicants argue as above that the teachings of Magnuson et al. does not represent production in compartments of a real plant as recited in the present claims (reply page 11)

The Examiner maintains as above that Applicants' arguments are directed to limitations that are not recited in the rejected claims. The rejected claims recite no limitations directed to the production of antibodies in the "compartments of a real plant"; rather, the rejected claims recite that production occurs in a "cellular compartment of a plant". The successful excretion of monoclonal antibody heavy chains in a tobacco cell suspension taught by Magnuson et al. necessarily requires the production of a heavy chain immunoglobulin in a plant cellular compartment, as excretion of proteins from cells requires their production in the endoplasmic reticulum cellular compartment prior to excretion.

Applicants argue as above that Casterman et al. is not an enabling disclosure (reply page 11).

The Examiner maintains as above that Casterman et al. is fully enabled, as evidenced by Hiatt et al.'s successful production of two different transgenic plant lines that express only immunoglobulin heavy chain polypeptides.

Applicants argue LeGall et al. does not make up for the deficiencies of Magnuson et al. and Casterman et al. since Le Gall et al. also provide no disclosure of heavy chain only antibodies in plants (reply pages 11-12).

The Examiner maintains that LeGall et al. was not cited for the disclosure of heavy chain only antibodies in plants. As set forth at pages 7-8 of the office action mailed April 8, 2004, Casterman et al. was cited for disclosing the expression in plants of heavy chain only antibodies, and LeGall et al. was cited for disclosing the expression in plants of a DNA sequence encoding a single-chain Fv recombinant immunoglobulin capable of specific binding with an antigen that is a plant pathogen, such that it would have been obvious to one skilled in the art at the time the invention was made to express in a plant any type of immunoglobulin capable of specific binding with an antigen that is a plant pathogen.

Claim 6 remains rejected under 35 U.S.C. 103(a) as being unpatentable over either of Magnuson et al. (Protein Expression and Purification, 1996, Vol. 7, pages 220-228) or Casterman et al. (WO 94/04678, 3 March 1994, Applicant's IDS), in view of Artsaenko et al. (The Plant Journal, Vol. 8, No. 5, pages 745-750, 1995), for the reasons of record set forth in the office action mailed April 8, 2004.

Applicants' arguments filed August 5, 2004, have been fully considered but they are not persuasive.

Applicants argue as above that the teachings of Magnuson et al. does not represent production in compartments of a real plant as recited in the present claims (reply page 12).

The Examiner maintains as above that Applicants' arguments are directed to limitations that are not recited in the rejected claims. The rejected claims recite no limitations directed to the production of antibodies in the "compartments of a real plant"; rather, the rejected claims recite that production occurs in a "cellular compartment of a plant". The successful excretion of

monoclonal antibody heavy chains in a tobacco cell suspension taught by Magnuson et al. necessarily requires the production of a heavy chain immunoglobulin in a plant cellular compartment, as excretion of proteins from cells requires their production in the endoplasmic reticulum cellular compartment prior to excretion.

Applicants argue as above that Casterman et al. is not an enabling disclosure (reply page 12).

The Examiner maintains as above that Casterman et al. is fully enabled, as evidenced by Hiatt et al.'s successful production of two different transgenic plant lines that express only immunoglobulin heavy chain polypeptides.

Applicants argue Artsaenko et al. does not make up for the deficiencies of Magnuson et al. and Casterman et al. since Artsaenko et al. also provide no disclosure of heavy chain only antibodies in plants (reply page 12).

The Examiner maintains that Artsaenko et al. was not cited for the disclosure of heavy chain only antibodies in plants. As set forth at pages 7-8 of the office action mailed April 8, 2004, Casterman et al. was cited for disclosing the expression in plants of heavy chain only antibodies, and Artsaenko et al. was cited for disclosing the expression in plants of a DNA sequence encoding a single-chain Fv recombinant immunoglobulin capable of specific binding with an antigen that is a plant hormone, such that it would have been obvious to one skilled in the art at the time the invention was made to express in a plant any type of immunoglobulin capable of specific binding with an antigen that is a plant hormone.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Remarks

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Cynthia Collins whose telephone number is (571) 272-0794. The examiner can normally be reached on Monday-Friday 8:45 AM -5:15 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Amy Nelson can be reached on (571) 272-0804. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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